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Abstract: PURPOSE: To evaluate whether F-fluoroethyltyrosine (FET) PET can discriminate progression from pseudoprogression of brain metastases in patients with non-small cell lung cancer undergoing immunotherapy and radiotherapy to the brain. METHODS: Retrospective analysis of F-FET PET scans in cases with documented progression of brain metastases on MRI in a cohort of 53 patients with non-small cell lung cancer receiving immune-checkpoint inhibitors and radiotherapy of brain metastases at the University Hospital of Zürich from June 2015 until January 2019. Response to radiotherapy was assessed by MRI. In case of equivocal findings and/or radiological progression in clinically asymptomatic patients, further assessment with F-FET PET was performed. RESULTS: From the cohort of 53 patients, the restaging MRI showed in 30 patients (56.6%) progression of at least 1 treated metastasis. Thereof, F-FET PET was performed in 11 patients, based on the absence of neurological symptoms or presence of systemic response and physicians' decision. F-FET PET correctly identified pseudoprogression in 9 of 11 patients (81.8%). In patients who did not undergo F-FET PET, 5 of 19 (26.3%) were diagnosed with pseudoprogression. CONCLUSIONS: Pseudoprogression of brain metastases occurred in 50% of patients diagnosed with progression on MRI. F-FET PET may help differentiate pseudoprogression from real progression in order to avoid discontinuation of effective therapy or unneeded interventions.

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^{18}F-FET PET for Diagnosis of Pseudoprogression of Brain Metastases in Patients With Non–Small Cell Lung Cancer

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Purpose: To evaluate whether ^{18}F-fluoroethyltyrosine (FET) PET can discriminate progression from pseudoprogression of brain metastases in patients with non–small cell lung cancer undergoing immunotherapy and radiotherapy to the brain.

Methods: Retrospective analysis of ^{18}F-FET PET scans in cases with documented progression of brain metastases on MRI in a cohort of 53 patients with non–small cell lung cancer receiving immune-checkpoint inhibitors and radiotherapy of brain metastases at the University Hospital of Zürich from June 2015 until January 2019. Response to radiotherapy was assessed by MRI. In case of equivocal findings and/or radiological progression in clinically asymptomatic patients, further assessment with ^{18}F-FET PET was performed.

Results: From the cohort of 53 patients, the restaging MRI showed in 30 patients (56.6%) progression of at least 1 treated metastasis. Thereof, ^{18}F-FET PET was performed in 11 patients, based on the absence of neurological symptoms or presence of systemic response and physicians' decision. ^{18}F-FET PET correctly identified pseudoprogression in 9 of 11 patients (81.8%). In patients who did not undergo ^{18}F-FET PET, 5 of 19 (26.3%) were diagnosed with pseudoprogression.

Conclusions: Pseudoprogression of brain metastases occurred in 50% of patients diagnosed with progression on MRI. ^{18}F-FET PET may help differentiate pseudoprogression from real progression in order to avoid discontinuation of effective therapy or unneeded interventions.

Key Words: ^{18}F-fluoroethyltyrosine PET (^{18}F-FET PET), brain metastases, immunotherapy, non–small cell lung cancer, pseudoprogression, radiotherapy

(*Clin Nucl Med* 2020;45: 113–117)

Recent phase III trials with immune-checkpoint inhibitors (ICIs) for advanced non–small cell lung cancer (NSCLC) included a small number of patients with stable and previously treated brain metastases.[1,2] Systemic pseudoprogression, defined as initial radiological enlargement of lesions followed by spontaneous decrease in size or stabilization, due to immune-cell infiltrate, is reported to occur in approximately 5% of NSCLC patients.[3–5] The Immunotherapy Response Assessment for Neuro-Oncology criteria have been developed to evaluate response to immunotherapy in the brain. Based on the Immunotherapy Response Assessment for Neuro-Oncology criteria, suspicion of progressive disease within 6 months after the start of immunotherapy (eg, tumor progression or appearance of new lesions) requires confirmation of tumor progression with further follow-up imaging, while immunotherapy should be continued until true progression is confirmed.[6] One case of pseudoprogression of brain metastases under immunotherapy has been described in a melanoma patient.[7] Pseudoprogression may also occur with gliomas after effective treatment.[8–11] High-dose radiotherapy as radiosurgery or stereotactic radiotherapy may induce pseudoprogression in 2% to 30% of cases.[12] Moreover, higher rates of symptomatic radiation necrosis have been reported after stereotactic radiotherapy in patients receiving immunotherapy.[13]

PET using ^{18}F-FDG as radiotracer is indicated for whole-body assessment of NSCLC patients but is not as useful for brain metastases, owing to high physiologic background activity there. O-(2-(^{18}F)-fluoroethyl)-L-tyrosine PET (^{18}F-FET PET) might discriminate pseudoprogression from real progression of brain lesions, based on uptake ratios and dynamic uptake patterns.[14] FET uptake occurs through large neutral amino acid transporters (LATs)[15] (Fig. 1), which are expressed on tumor cells and immune cells. Fluoroethyltyrosine is transported by LAT2, which is not expressed in inflammatory cells, but to a high extent on tumor cells (Fig. 2). Thus, FET is selectively taken up by tumor cells, which[16–18] advocates FET as a valuable tracer for the discrimination of neoplastic and inflammatory lesions.[19,20]

The aim of this study was to evaluate the ability of ^{18}F-FET PET to distinguish pseudoprogression from real progression of brain metastases in NSCLC patients treated with radiotherapy and immunotherapy.

PATIENTS AND METHODS

Study Design and Patients

We evaluated the use of ^{18}F-FET PET in cases with documented progression of brain metastases on MRI in a retrospective cohort of 53 patients with NSCLC receiving ICIs and radiotherapy of brain metastases at the University Hospital of Zürich between June 2015 and January 2019. Our study was approved by the local ethics committee (EK-ZH-2017-00152 and EK-ZH-2018-01919) and is in accordance with local laws and regulations.

Imaging

All MRIs were performed as standard of care between 6 and 8 weeks after the last radiotherapy, including the following pulse sequence set: T2-weighted, FLAIR-weighted, susceptibility-weighted, T1-weighted with and without gadolinium contrast and

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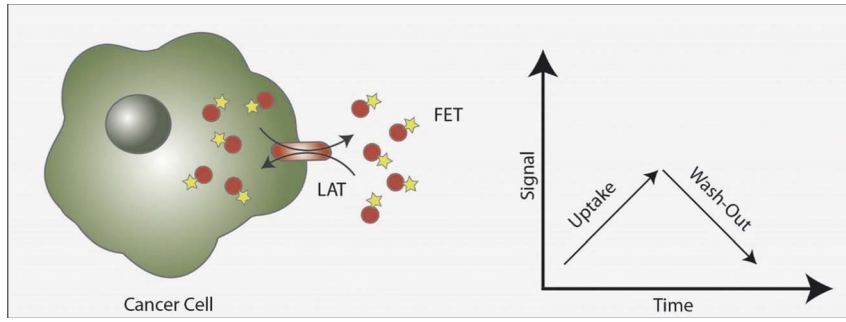

FIGURE 1. Fluoroethyltyrosine uptake through LAT transporter on vital tumor cell.

diffusion-weighted images (Skyra Magnetom 3 T [Siemens, Forchheim, Germany]; Ingenia 3 T [Philips, Best, The Netherlands]).

^{18}F-FET PET examinations were acquired using a Discovery 690 Standard scanner (GE Healthcare, Waukesha, WI) or a Signa PET/MR scanner (GE Healthcare). A standardized dose of 130 MBq of ^{18}F-FET was injected. The dynamic ^{18}F-FET PET acquisition started either immediately (PET/MR) or at 20 minutes after tracer injection (PET/CT), using eight or four 5-minute frames, respectively. For assessing the dynamic ^{18}F-FET uptake pattern, the 4 frames from 20 to 40 minutes were plotted, following the recommendation of the 2018 joint Response Assessment in Neuro-oncology/European Association of Neuro-Oncology/European Association of Nuclear Medicine guidelines.[21–24] The dynamic FET uptake pattern, SUVmax, and mean and maximum target-to-background ratio (TBRmean, TBRmax), as well as time-to-peak (TTP) were analyzed. Based on previous publications,[25,26] the following parameters were considered to indicate progression rather than pseudoprogression: TBRmean greater than 1.95 with ^{18}F-FET washout or plateau uptake pattern or TBRmax greater than 2.55, regardless of uptake pattern, as well as a shorter TTP. Follow-up MRI was routinely performed 4 to 8 weeks after ^{18}F-FET PET.

RESULTS

Forty-one (77.4%) patients had adenocarcinoma, 9 (17%) had squamous cell carcinoma, 2 (3.8%) had undifferentiated carcinoma, and 1 (1.9%) had large cell neuroendocrine carcinoma. Thirty-three patients (62.3%) were treated with nivolumab, 12 (22.6%) with pembrolizumab, 5 (9.4%) with ipilimumab-nivolumab, 2 (3.8%) with atezolizumab, and 1 (1.9%) with nivolumab and anti–LAG-3 antibody. Twenty-three patients (43.4%) were alive at the last follow-up, and 30 (56.6%) died due to NSCLC. Among these 23 alive patients, 11 (47.8%) had a metabolic complete remission of systemic disease, 10 (43.5%) were in partial remission, and 2 (8.7%) had progressive disease at the end of follow-up. The median overall survival from the beginning of immunotherapy was 17.7 months (95% confidence interval, 13.4–22.1 months). The median overall survival among the 23 alive patients was 20.7 months (range, 2.49–44.3 months).

All patients underwent radiotherapy for brain metastases. Thirty-two (60.4%) received a single course, 16 (30.2%) received 2 courses, and 5 (9.4%) received 3 or more, with a total of 80 treatments performed. Forty-three treatments (53.7%) consisted of radiosurgery, 25 (31.3%) of hypofractionated stereotactic radiotherapy, and 12 (15%) of whole-brain radiotherapy.

From the cohort of 53 patients, an MRI after radiotherapy showed in 30 patients (56.6%) progression of at least 1 treated metastases, and in 18 (34.0%) cases a partial response based on the Response Assessment in Neuro-oncology–Brain Metastases criteria. Of the 30 patients with MRI-documented progression, ^{18}F-FET PET was performed in 11 subjects, between 2 and 4 weeks after the MRI. The decision of acquiring an ^{18}F-FET PET was based on the absence of neurological symptoms or presence of systemic response and physicians' decision. No additional MRI criteria were used. In 9 of 11 patients (81.8%), ^{18}F-FET PET suggested pseudoprogression rather than progression, which was confirmed by MRI 4 to 8 weeks later. In 1 of 11 patients (9.1%), ^{18}F-FET PET suggested true progression, which was, however, not confirmed by follow-up MRIs during 20 months.

In the remaining subject (9.1%), ^{18}F-FET PET results were inconclusive because of borderline TBRmax and a plateau pattern in the dynamic images; this case was confirmed as true progression at follow-up (Figs. 3A–D, Figs. 4A–C).

Of the 19 patients, where no ^{18}F-FET PET was performed, follow-up MRI showed pseudoprogression in 5 cases (26.3%) (Fig. 4).

Altogether, from 30 patients with initial MRI-based diagnosis of progression, 50% had a pseudoprogression (Fig. 5). The median follow-up time after ^{18}F-FET PET was 7.8 months (range,

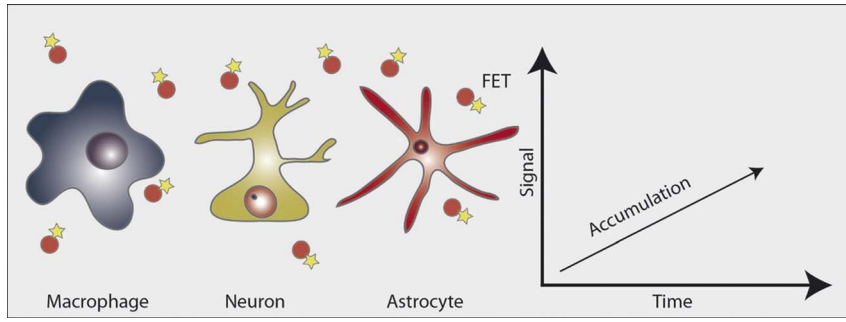

FIGURE 2. Lack of active uptake of FET into inflammatory and normal brain tissue, extracellular accumulation by disrupted blood-brain barrier.

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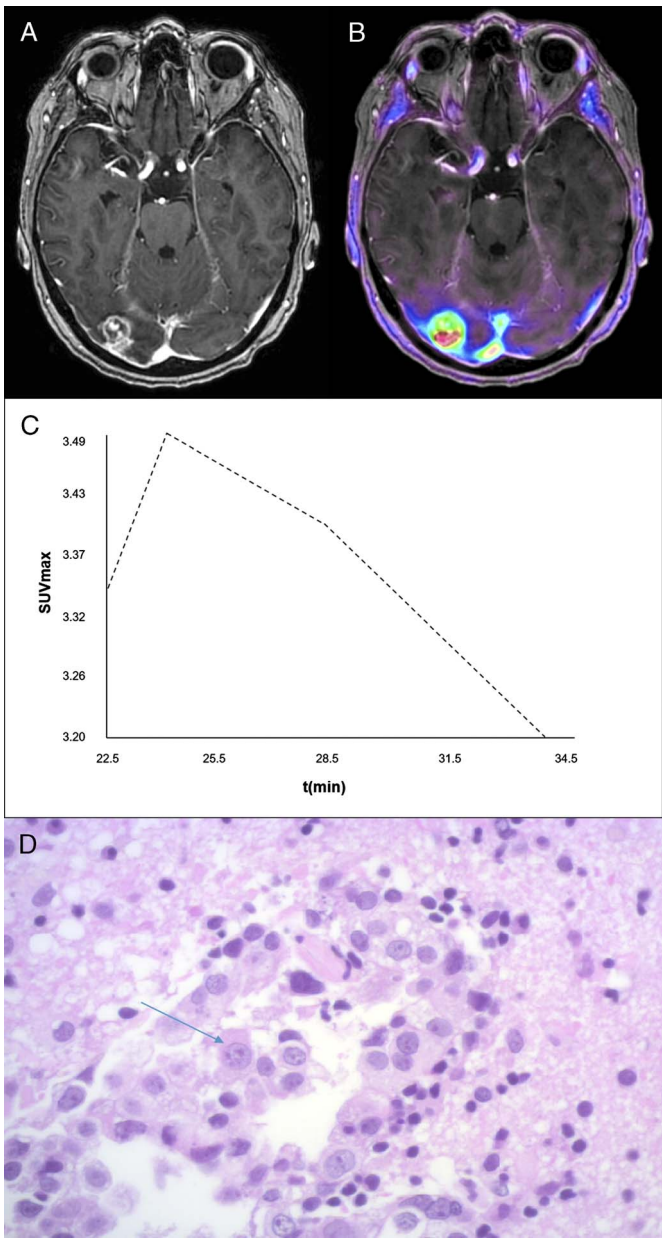

FIGURE 3. A and B, MRI and ^{18}F-FET PET/MRI images of a patient with real progression. C, Dynamic ^{18}F-FET "washout" pattern of the same patient. D, Small clusters of epithelial tumor cells (arrow) within reactive brain parenchyma in resected brain metastasis from the same patient.

2.3–47 months). During this period, follow-up MRIs were performed at least every 3 months.^{18}F-FET PET parameters are listed in Table 1.

DISCUSSION

Suspicion of progression of brain metastases may lead to discontinuation of an effective therapy, for example, immunotherapy, or provoke unneeded interventions. In our cohort of 30 patients with initially suspected progression in MRI, 23 were alive at the end of follow-up, thereof 11 (47.8%) had a complete remission of systemic disease and 10 (43.5%) were in good partial remission under continuing treatment with ICIs at the end of follow-up. It is therefore of paramount importance to use tools that accurately identify pseudoprogression in patients undergoing immunotherapy.

Pseudoprogression of brain lesions, observed as radiological enlargement followed by spontaneous decrease in size or stabilization, may occur after effective treatment, such as immunotherapy, radiation therapy, or a combination of both. In our cohort, all patients received both immunotherapy and brain irradiation; hence, observed pseudoprogressions in our cohort may be regarded as radiation necrosis. Martin et al[13] have reported higher rates of radiation necrosis in patients undergoing brain-directed radiotherapy and simultaneous systemic immunotherapy.

The MRI-based assessment of irradiated brain metastases is challenging. Metastases typically cause a disruption of the blood-brain barrier, leading to contrast enhancement on MRI. The same mechanism is responsible for contrast enhancement of radionecrosis, making the differentiation between real progression and pseudoprogression difficult.

Perfusion-weighted MRI with dynamic susceptibility contrast technique is one of the most important methods to discriminate progression from radionecrosis.[18] The relative cerebral blood volume was shown useful in the distinction of active tumor lesions and radionecrosis, with tumor exhibiting higher relative cerebral blood volume. Nevertheless, hypoxia due to radiation necrosis may also induce neoangiogenesis, making a proper distinction difficult.[27] MRI spectroscopy using ratios of choline/creatine and/or choline/N-acetyl aspartate may contribute to a better distinction of radionecrosis, but is limited in small lesions and in the posterior fossa.[18,28] A combination of ^{18}F-FET PET and perfusion-weighted MRI was shown to improve

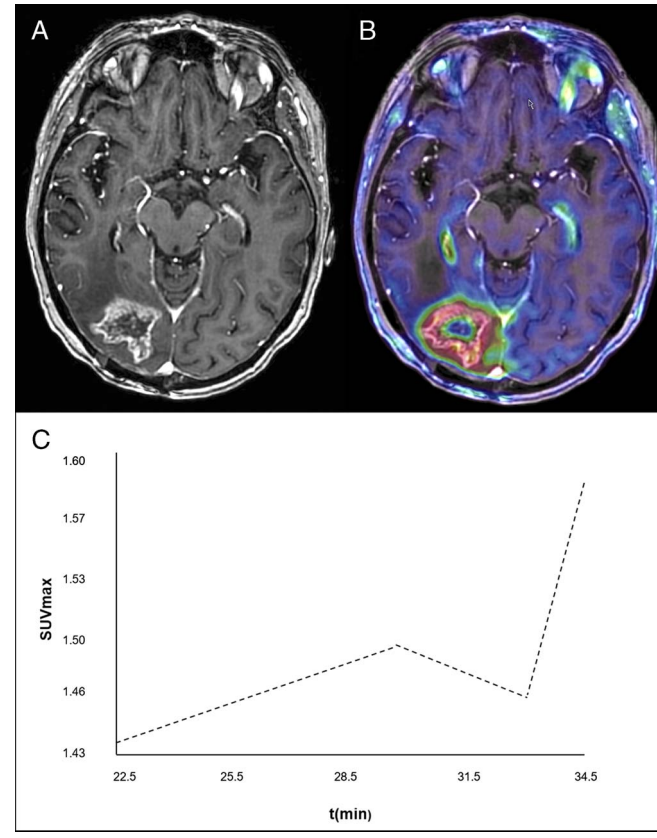

FIGURE 4. A and B, MRI and ^{18}F-FET PET/MRI images of a patient with pseudoprogression. C, Dynamic ^{18}F-FET "wash-in" pattern of the same patient.

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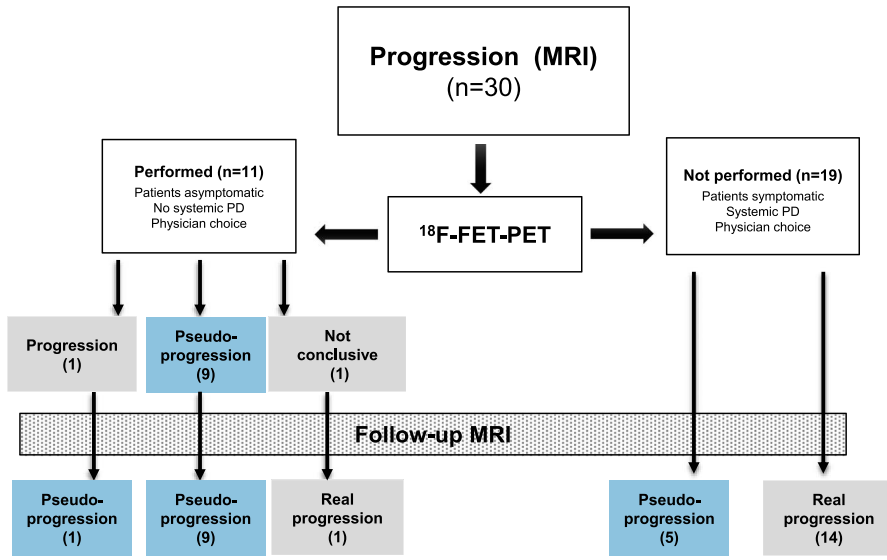

FIGURE 5. Flowchart on response assessment with MRI and ^{18}F-FET PET in NSCLC patients with brain metastases. In 30 of 53 (56.6%) patients, progression on MRI was diagnosed. In 11 of these 30 patients (36.7%), ^{18}F-FET PET was performed. In 19 (63.3%), no ^{18}F-FET PET was performed.

the accuracy of glioma grading compared with MRI alone.[29] Specific literature data on the use of this combined technique for radiation necrosis vs vital brain metastases are currently lacking.

^{18}F-FET PET data are acquired dynamically during a comparably long time of at least 20 minutes. A continuous slow accumulation of tracer typically represents a disrupted blood-brain barrier, with the radiotracer being trapped in the interstitium. On the other hand, a rapid early uptake followed by washout of activity represents active transport, requiring vital tumor tissue.

In our series, pseudoprogression occurred in 50% of patients, who were previously diagnosed as progressive on MRI. This is a fundamental information for clinicians who may safely continue treatment without additional intervention on brain metastasis. In our study, ^{18}F-FET PET, where performed, identified 90% of patients with pseudoprogression.

The limitations of our study are the comparably small number of patients and the clinical preselection of subjects who underwent ^{18}F-FET PET, which relied on systemic response and absence of neurological symptoms. Another limitation is that we do not report on perfusion-weighted MRI. This is owing to our study design, because MRI (partly perfusion-weighted MRI) was used as identifier of progression before ^{18}F-FET PET.

Our study indicates that the response assessment of brain metastases might require a closer investigation, as the expected rate of pseudoprogression in patients treated with both radiotherapy and immunotherapy is much higher compared with the rate expected after radiotherapy alone. This is the first study to investigate the role of ^{18}F-FET PET in NSCLC patients treated with immunotherapy and radiotherapy for brain metastases, providing new insights about intracranial response and strong evidence for the use of this diagnostic tool.

TABLE 1. Summary of ^{18}F-FET PET Findings

Patient	FET PET Conclusion	Progression at Follow-up*	Target Lesions†	SUVmax	SUVmean	TBRmax	TBRmean	TTP
1	Pseudoprogression	No	2	3.0/3.4	2.6/2.7	2.1/2.4	1.9/1.9	7.5/7.5
2	Pseudoprogression	No	1	1.7	1.7	1.9	1.9	17.5
3	Pseudoprogression	No	2	1.4/1.8	1.4	1.6/2.0	1.6/1.8	17.5/17.5
4	Pseudoprogression/ inconclusive	Yes	4	2.7/2.8/3.3	2.7/2.7/3.1	1.4/1.4/1.7	1.4/1.4/1.6	17.5/17.5/17.5
5	Pseudoprogression	No	2	3.5/3.7	3.0/2.8	2.5/2.6	2.1/2.0	17.5/17.5
6	Real progression	No	2	3.3/3.2	2.5/2.9	3.7/3.6	2.8/3.2	7.5/7.5
7	Pseudoprogression	No	2	2.5/1.8	2.2/1.7	2/1.4	1.7/1.3	40
8	Pseudoprogression	No	1	2.2	1.8	2.0	1.6	17.5
9	Pseudoprogression	No	2	5.1/4.7	3.2	3.6/2.3	2.3	40
10	Pseudoprogression	No	2	2.7/2.6	2.2	3.4/3.3	2.8	40
11	Pseudoprogression	No	1	1.4	1.2	1.9	1.6	40

*Progression or brain metastases as assessed per follow-up MRI.

†Brain metastases treated with radiotherapy and assessed with ^{18}F-FET PET.

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Based on our data, we have designed a prospective clinical trial comparing the use of MRI and ^{18}F-FET PET in this population of patients.

REFERENCES

1. Brahmer J, Reckamp KL, Baas P, et al. Nivolumab versus docetaxel in advanced squamous-cell non–small-cell lung cancer. *N Engl J Med*. 2015; 373:123–135.
2. Reck M, Rodriguez-Abreu D, Robinson AG, et al. Pembrolizumab versus chemotherapy for PD-L1–positive non–small-cell lung cancer. *N Engl J Med*. 2016;375:1823–1833.
3. Curioni-Fontecedro A, Ickenberg C, Franzen D, et al. Diffuse pseudoprogression in a patient with metastatic non-small-cell lung cancer treated with nivolumab. *Ann Oncol*. 2017;28:2040–2041.
4. Eshghi N, Lundeen TF, Kuo PH. Dynamic adaptation of tumor immune response with nivolumab demonstrated by ^{18}F-FDG PET/CT. *Clin Nucl Med*. 2018;43:114–116.
5. Beer L, Hochmair M, Haug AR, et al. Comparison of RECIST, iRECIST, and PERCIST for the evaluation of response to PD-1/PD-L1 blockade therapy in patients with non–small cell lung cancer. *Clin Nucl Med*. 2019;44: 535–543.
6. Okada H, Weller M, Huang R, et al. Immunotherapy response assessment in neuro-oncology: a report of the RANO working group. *Lancet Oncol*. 2015; 16:e534–e542.
7. Cohen JV, Alomari AK, Vortmeyer AO, et al. Melanoma brain metastasis pseudoprogression after pembrolizumab treatment. *Cancer Immunol Res*. 2016;4:179–182.
8. Katsanos AH, Alexiou GA, Fotopoulos AD, et al. Performance of ^{18}F-FDG, ^{11}C-methionine, and ^{18}F-FET PET for glioma grading: a meta-analysis. *Clin Nucl Med*. 2019.
9. Vettermann FJ, Felsberg J, Reifenberger G, et al. Characterization of diffuse gliomas with histone H3-G34 mutation by MRI and dynamic ^{18}F-FET PET. *Clin Nucl Med*. 2018;43:895–898.
10. Galldiks N, Schroeter M, Fink GR, et al. Interesting image. PET imaging of a butterfly glioblastoma. *Clin Nucl Med*. 2010;35:49–50.
11. Galldiks N, Brunn A, Fink GR, et al. Dynamic FET PET imaging of a "butterfly" IDH-wildtype anaplastic astrocytoma. *Clin Nucl Med*. 2019;44: e581–e582.
12. Kohutek ZA, Yamada Y, Chan TA, et al. Long-term risk of radionecrosis and imaging changes after stereotactic radiosurgery for brain metastases. *J Neurooncol*. 2015;125:149–156.
13. Martin AM, Cagney DN, Catalano PJ, et al. Immunotherapy and symptomatic radiation necrosis in patients with brain metastases treated with stereotactic radiation. *JAMA Oncol*. 2018;4:1123–1124.
14. Galldiks N, Stoffels G, Filss CP, et al. Role of O-(2-(18)F-fluoroethyl)-L-tyrosine PET for differentiation of local recurrent brain metastasis from radiation necrosis. *J Nucl Med*. 2012;53:1367–1374.
15. Habermeier A, Graf J, Sandhofer BF, et al. System L amino acid transporter LAT1 accumulates O-(2-fluoroethyl)-L-tyrosine (FET). *Amino Acids*. 2015; 47:335–344.
16. Sun A, Liu X, Tang G. Carbon-11 and fluorine-18 labeled amino acid tracers for positron emission tomography imaging of tumors. *Front Chem*. 2018; 5:124.
17. Spaeth N, Wyss MT, Weber B, et al. Uptake of ^{18}F-fluorocholine, ^{18}F-fluoroethyl-L-tyrosine, and ^{18}F-FDG in acute cerebral radiation injury in the rat: implications for separation of radiation necrosis from tumor recurrence. *J Nucl Med*. 2004;45:1931–1938.
18. Chuang MT, Liu YS, Tsai YS, et al. Differentiating radiation-induced necrosis from recurrent brain tumor using MR perfusion and spectroscopy: a meta-analysis. *PLoS One*. 2016;11:e0141438.
19. Hutterer M, Nowosielski M, Putzer D, et al. [^{18}F]-fluoro-ethyl-L-tyrosine PET: a valuable diagnostic tool in neuro-oncology, but not all that glitters is glioma. *Neuro Oncol*. 2013;15:341–351.
20. Langen KJ, Hamacher K, Weckesser M, et al. O-(2-[^{18}F]fluoroethyl)-L-tyrosine: uptake mechanisms and clinical applications. *Nucl Med Biol*. 2006;33:287–294.
21. Ceccon G, Lohmann P, Stoffels G, et al. Dynamic O-(2-^{18}F-fluoroethyl)-L-tyrosine positron emission tomography differentiates brain metastasis recurrence from radiation injury after radiotherapy. *Neuro Oncol*. 2017;19: 281–288.
22. Tscherpel C, Dunkl V, Ceccon G, et al. The use of O-(2-^{18}F-fluoroethyl)-L-tyrosine PET in the diagnosis of gliomas located in the brainstem and spinal cord. *Neuro Oncol*. 2017;19:710–718.
23. Albatly AA, Alsamarah AT, Alhawas A, et al. Value of (18)F-FET PET in adult brainstem glioma. *Clin Imaging*. 2018;51:68–75.
24. Law I, Albert NL, Arbizu J, et al. Joint EANM/EANO/RANO practice guidelines/SNMMI procedure standards for imaging of gliomas using PET with radiolabelled amino acids and [^{18}F]FDG: version 1.0. *Eur J Nucl Med Mol Imaging*. 2019;46:540–557.
25. Albert NL, Weller M, Suchorska B, et al. Response Assessment in Neuro-oncology Working Group and European Association for Neuro-Oncology recommendations for the clinical use of PET imaging in gliomas. *Neuro Oncol*. 2016;18:1199–1208.
26. Kebir S, Rauschenbach L, Galldiks N, et al. Dynamic O-(2-[^{18}F] fluoroethyl)-L-tyrosine PET imaging for the detection of checkpoint inhibitor-related pseudoprogression in melanoma brain metastases. *Neuro Oncol*. 2016;18:1462–1464.
27. Vellayappan B, Tan CL, Yong C, et al. Diagnosis and management of radiation necrosis in patients with brain metastases. *Front Oncol*. 2018;8:395.
28. Muto M, Frauenfelder G, Senese R, et al. Dynamic susceptibility contrast (DSC) perfusion MRI in differential diagnosis between radionecrosis and neoangiogenesis in cerebral metastases using rCBV, rCBF and K2. *Radiol Med*. 2018;123:545–552.
29. Verger A, Filss CP, Lohmann P, et al. Comparison of (18)F-FET PET and perfusion-weighted MRI for glioma grading: a hybrid PET/MR study. *Eur J Nucl Med Mol Imaging*. 2017;44:2257–2265.

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